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Regional hyperperfusion in cognitively normal *APOE* 4 allele carriers in mid-life: analysis of ASL pilot data from the PREVENT-Dementia cohort

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ABSTRACT:

Background: Regional cerebral hypoperfusion is characteristic of Alzheimer's disease (AD). Previous studies report conflicting findings in cognitively-normal individuals at high risk of AD. Understanding early preclinical perfusion alterations may improve understanding of AD pathogenesis and lead to new biomarkers and treatment targets.

Methods: 3T arterial spin labelling MRI scans from 162 participants in the PREVENT-Dementia cohort were analysed (cognitively normal participants aged 40-59, stratified by future dementia risk). Cerebral perfusion was compared vertex-wise according to *APOE* 4 status and family history (FH). Correlations between individual perfusion, age and cognitive scores (COGNITO battery) were explored.

Results: Regional hyperperfusion was found in *APOE* 4+ group (left cingulate and lateral frontal and parietal regions $p < .01$, TFCE) and in FH+ group (left temporal and parietal regions $p < .01$, TFCE). Perfusion did not correlate with cognitive test scores.

Conclusions: Regional cerebral hyperperfusion in individuals at increased risk of AD in mid-life may be a very early marker of functional brain change related to AD. Increased perfusion may reflect a functional ‘compensation’ mechanism, offsetting the effects of early neural damage, or may itself be risk factor for accelerating spread of degenerative pathology.

Key words: Alzheimer’s disease, *APOE 4*, Family history, Magnetic Resonance Imaging (MRI), Arterial Spin Labelling (ASL), Cerebral Blood Flow (CBF), Cerebral hyperperfusion

BACKGROUND:

Some changes in the brain, such as increased amyloid deposition, precede cognitive changes in Alzheimer's disease (AD) by years or decades and early identification of such changes may allow treatments to be targeted towards this early stage before gross brain damage occurs[1]. Brain function may also differ in at-risk individuals prior to any clinically identifiable deterioration in cognition or behaviour and could potentially further elucidate the natural history of the disease or be used to identify or predict conversion to a disease state. While these early changes are becoming well established for amyloid, they are less clear for other changes, especially functional changes such as blood flow. Though studies of familial AD indicate functional neuroimaging may be useful in this regard, more evidence is needed in sporadic late onset AD[2].

Arterial spin labelling (ASL) MRI is a non-invasive perfusion imaging technique for the measurement of cerebral blood flow (CBF). A radio frequency (RF) pulse is used to invert the magnetisation of water protons in a slab typically situated at the level of the carotids. After a short delay, sufficient to allow the 'labelled' blood to reach tissues of interest in the brain, a 'tag' image is acquired. This is subtracted from a 'control' image resulting in an image showing tissue perfusion[3]. Patterns of CBF produced with ASL have been shown to agree closely with those from perfusion single-photon emission computed tomography (SPECT) and metabolic positron emission tomography (PET) in healthy controls and patient groups[4,5]. SPECT and PET are well-established AD imaging markers and FDG-PET is included in the most recent diagnostic criteria for AD[6]. An established pattern of perfusion deficits measured using ASL is recognised in AD, with hypoperfusion most marked in the precuneus, posterior cingulate and superior parietal cortex and less prominently in the lateral frontal cortex, orbitofrontal cortex and temporal lobe structures including the hippocampus and parahippocampus[7].

Relatively few studies have investigated differences in CBF between cognitively normal adults with and without risk factors for AD such as *APOE* 4 and family history (FH). Findings have been somewhat mixed; for example, Fleisher et al.[8] and Bangen et al.[9] found increased resting CBF in the medial temporal lobe in cognitively-normal participants who carried *APOE* 4. Wierenga et al.[10] found patterns of hypoperfusion similar to those in MCI and AD in cognitively normal older *APOE* 4 carriers but areas of hyperperfusion in

younger *APOE* 4 carriers. However, Chandler et al.[11] found reduced mean grey matter CBF in young *APOE* 4 carriers. In a larger study Okonkwo et al.[12] found no effect of *APOE* status on CBF but found that at mid-life those with a maternal FH of AD had perfusion deficits reminiscent of those seen in MCI and AD participants. Therefore, a consensus on the impacts of age, *APOE* 4 and FH has not yet been reached.

CBF derived from ASL may be a promising functional candidate marker for AD as it has predictive value for cognitive decline and conversion from MCI to AD[13]. As ASL is non-invasive and does not use ionising radiation there are evident advantages to using this tool in research and clinical populations, since scans can be repeated over time without carcinogenic risk. In order to address the limited and mixed evidence from the literature ASL data was collected from cognitively normal individuals in mid-life recruited as part of the PREVENT-Dementia cohort. These individuals could be stratified for their risk of developing AD based on their family history and *APOE* allele carrier status. We hypothesised that changes in CBF would be seen in key regions of the brain in individuals at increased risk of developing AD and that such regions would include the cingulate gyrus and medial temporal lobe.

METHODS:

Participants: 210 cognitively normal men and women aged 40-59 years were recruited for the PREVENT-Dementia cohort[14] via a locally-held database of research volunteers[15] and underwent assessment with the aim of identifying AD biomarkers in cognitively normal individuals in mid-life. Assessment included a structured interview to elicit neuropsychiatric symptoms and to determine life-style factors. A computerised neuropsychometric battery (COGNITO) was administered[16]. Physical examination was performed and blood samples collected to determine *APOE* status. A Dementia Risk Score (DRS) was calculated for each participant. This validated score (from the CAIDE study[17]) includes age, gender, years of education, systolic blood pressure, BMI, serum cholesterol and level of physical activity. The 18-point version incorporates *APOE* 4 allele carrier status, while the 15-point version does not; both forms of the scale were calculated. FH of dementia (defined as having at least one parent with a dementia diagnosis) was recorded. Of the 210 participants, 17 declined or had contraindications to MRI scanning, therefore 193 participants underwent scanning.

Magnetic resonance imaging:

Images were acquired using a Siemens Verio 3T MRI scanner. The following acquisitions were performed as part of a multi-modal MR examination: whole brain T1-weighted scan (MPRAGE, 160 slices, voxel size 1.0mm³, TR=2300ms, TE=2.98ms, FA=9°); ASL (PICORE Q2T, 50 pairs of control/ tag images, TR=2500ms, TE=11ms, inversion time=1800ms, bolus duration=700ms, voxel size 3.0x3.0x6.0mm, axial slices=14, slice gap=1.5mm, FA=90°).

ASL scans were quality controlled by visual inspection, scans were excluded due to ASL-related artefacts (e.g. fat saturation artefact and labelling asymmetry), brain abnormalities such as tumour, or if field of view (FOV) was inadequate. FOV was judged to be inadequate if any of the superior or posterior aspect was cropped or if cropping of the inferior aspect impinged on the hippocampus which was defined according to the Desikan-Killiany atlas. See *figure 1* for scan inclusion/ exclusion pathway. ASL data from 162/193 (83.9%) individuals were available for analysis.

Image analysis ASL:

Image post-processing was performed using FSL's Bayesian Inference for ASL MRI (BASIL) toolbox[18] and the FreeSurfer image analysis suite (V6.0.0 <http://surfer.nmr.mgh.harvard.edu/>). As part of the BASIL pipeline, the acquired ASL scans were motion corrected using FSL's MCFLIRT and calibrated based on a proton density acquisition. CBF was quantified using the Buxton ASL kinetic model[19]. FreeSurfer was used to segment the individual T1 images into white and grey matter and CSF; individual ASL CBF maps were then co-registered to individual T1 images using a boundary-based registration algorithm[20] and projected onto the cortical ribbon. FreeSurfer uses surface-based (rather than volume-based) registration and smoothing which has been shown in PET (with similar resolution to ASL) to improve signal to noise ratio (SNR), to reduce contamination of the grey matter signal with signal from white matter and cerebrospinal fluid[21] and to reduce mixing of grey matter signal originating from distinct cortical areas during the smoothing process[22]. The cortical ASL maps were smoothed with FWHM of 8. Regional CBF and regional cortical thickness values were extracted for each individual using FreeSurfer[23].

Statistical analysis: Alpha was set at 0.05 for all tests. Statistical analyses were performed using SPSS [IBM Corp. Released 2018. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp.] and FSL[24]. Participants were grouped according to *APOE 4* allele carrier status and FH (both + vs -). Between group differences for age, gender, years of education, DRS score, FH (for the *APOE* groups), *APOE* status (for the FH groups), cognitive scores and mean cortical thickness were investigated. Age, years of education, DRS scores and cognitive test scores were found to have non-parametric distributions (normality tested using Shapiro-Wilk tests and Q-Q plots) and these nominal values were compared between groups using Mann-Whitney U test. The categorical values of gender and *APOE 4* status were compared using Chi-squared tests.

Regional CBF was compared between groups in a vertex-wise analysis using the Permutation Analysis of Linear Models (PALM) tool in FSL[25] with age, gender and years of education as covariates. This approach corrects for multiple comparisons (family-wise error correction (FWE)) in a data-driven manner using threshold-free cluster enhancement (TFCE) thus avoiding the inevitable arbitrary choices which must be made when applying vertex- and

cluster-wise thresholds; this means that TFCE is also reported to be more sensitive to genuine group differences[26]. The FH group comparison was also made with the additional covariate of *APOE* status in order to explore the contribution of possible hereditary factors other than *APOE* 4.

Relationships between CBF and age, years of education, DRS, cognitive test results and cortical thickness were assessed in the whole cohort in a vertex-wise correlation using PALM-FSL.

RESULTS:

Demographics: Groups were well-matched for age, gender and years of education (table 1).

There was a trend towards a greater number of *APOE* 4 carriers in the FH+ group but this difference did not reach statistical significance. DRS was significantly higher in the *APOE* 4 + group than *APOE* 4 – group and in the FH+ group than FH- group; the significant difference persisted for FH group but not *APOE* group when the contribution of *APOE* status to the DRS was removed (15-point DRS). The *APOE* 4+ group performed slightly better in the narrative recall task than the *APOE* 4- group; this was the only significant difference in cognitive test scores between groups. There was no difference in gross structural MR measures between groups, as measured by mean cortical thickness (table 2).

Table 1: demographics and group comparisons

		<i>APOE</i> 4 groups				FH groups			
	Whole cohort [n=162]	<i>APOE</i> 4+ [n=61]	<i>APOE</i> 4- [n=101]	Group difference	Sig.	FH+ [n=74]	FH- [n=88]	Group difference	Sig.
Age mean (SD)	51.8 (+/- 5.5)	51.0 (+/- 5.5)	52.4 (+/- 5.5)	MWU= 2585.5 Z= -1.7	.087	52.7 (+/- 4.5)	51.2 (+/- 6.1)	MWU= 2889.5 Z= -1.2	.218
Gender (m= male f= female)	m= 44 f= 118	m= 17 f= 44	m= 27 f= 74	X2= 0.03 df1	.875	m=18 f=56	m=26 f=62	X2= 0.55	.457
<i>APOE</i> 4 carrier status	pos= 61 neg= 101	NA	NA	NA	NA	pos= 33 neg= 41	pos=28 neg= 60	X2= 2.80	.095
Years of education mean (SD)	16.0 (+/- 3.5)	16.4 (+/- 3.2)	15.8 (+/- 3.6)	MWU= 2771.5 Z= -1.1	.283	15.9 (+/- 3.1)	16.2 (+/- 3.8)	MWU= 3092 Z= -0.6	.579
Parental dementia	pos= 74 neg= 88	pos= 33 neg= 28	pos= 41 neg= 60	X2= 2.80 df1	.095	NA	NA	NA	NA
18-point DRS mean (SD)	5.7 (+/- 2.9)	6.7 (+/- 2.5)	5.2 (+/- 2.9)	MWU= 2046 Z= -3.6	<.001**	6.5 (+/- 2.5)	5.1 (+/- 3.0)	MWU= 2349 Z= -3.1	.002**
15-point DRS mean (SD)	4.5 (+/- 2.4)	4.2 (+/- 2.2)	4.6 (+/- 2.6)	MWU= 2804.5 Z= -1.0	.332	5.0 (+/- 2.2)	4.0 (+/- 2.6)	MWU= 2525 Z= -2.5	.013*
Cognitive test scores (only significant findings)									
Narrative recall mean (SD)	NA	28.1 (+/- 7.6)	25.0 (+/- 8.3)	MWU= 2443 Z= -2.2	p=0.027*	-	-	nil	NA

DRS = dementia risk score (18-point score includes *APOE* 4, 15-point score does not take *APOE* 4 into account); MWU=Mann-Whitney U; X2=Chi-squared; *p<.05, **p<.01

Table 2: mean cortical thickness

		<i>APOE</i> 4 groups			FH groups		
	Whole cohort [n=162]	<i>APOE</i> 4+ [n=61]	<i>APOE</i> 4- [n=101]	Group difference (sig)	FH+ [n=74]	FH- [n=88]	Group difference (sig)
Mean cortical thickness in mm (SD)	2.46 (.07)	2.46 (.07)	2.45 (.06)	t= -.37 (p=.72)	2.46 (.06)	2.46 (.08)	t= .46 (p=.65)

Parental dementia diagnoses:

74 participants reported at least 1 parent with a dementia diagnosis; of these 7 participants (9.5%) reported 2 parents with a dementia diagnosis. Of all the parental diagnoses (n=81) the breakdown was: 70.4% Alzheimer's disease or mixed (Alzheimer's and vascular) dementia, 17.3% vascular dementia, 2.5% Frontotemporal dementia, 1.2% dementia with Lewy bodies, 1.2% Parkinson's disease dementia, (4.9% "unknown").

APOE 4 group comparisons:

Significant clusters of increased CBF were found in the *APOE* 4+ group in left and right hemispheres compared to the *APOE* 4- group with correction for age, gender, years of education and multiple comparisons (FWE) (*figure 2*). The largest effects were seen in the left cingulate and left lateral frontal and parietal regions.

FH group comparisons:

Significant clusters of increased CBF were found in left and right hemispheres in the FH+ group compared to the FH- group with correction for age, gender, years of education and multiple comparisons (FWE) (*figure 3*). The distribution and extent of these clusters were similar to those seen in the *APOE* group comparison but the largest effects were seen in the left lateral temporoparietal region and left temporal pole. When additional correction for *APOE* status was applied this region of hyperperfusion persisted but the effect size was reduced (*figure 4*).

Correlations:

No significant correlations were found between CBF and age, years of education, DRS or cognitive test scores.

DISCUSSION:

As hypothesised, we found differences in regional cerebral perfusion between cognitively normal individuals in mid-life at higher and lower risk of AD. We found differences in regional brain perfusion between *APOE* 4+ and *APOE* 4- groups and FH+ and FH- groups when corrected for age, gender, years of education and multiple comparisons (FWE).

Individuals in the PREVENT-Dementia cohort are of normal cognition and in mid-life. We did not find any group difference in mean cortical thickness between groups and the only significant group difference in terms of cognitive scores was in the narrative recall task where the *APOE* 4+ group scored slightly better than the *APOE* 4- group. Therefore, differences in perfusion are seen in the absence of gross structural brain changes, clinical disease or of prodromal (i.e. symptomatic) disease state. When additional correction for *APOE* status was applied to the FH group comparison the effect size of the group difference was much reduced, suggesting that hyperperfusion in this group may largely, but not exclusively, be driven by the effects of *APOE* 4. We found no significant difference in DRS between *APOE* 4+ and *APOE* 4- groups when *APOE* status was not included in the calculation and no correlation between regional CBF and DRS across all participants. These findings suggest that cardiovascular risk factors are not driving the difference in regional CBF between *APOE* 4+ and – groups.

We found higher CBF in the *APOE* 4+ group in widespread areas; with the largest effect sizes seen in the left cingulate cortex and left lateral frontal and parietal regions. The cingulate is an area where early changes are seen in AD; reduced perfusion in the precuneus and posterior cingulate cortex are the most commonly reported findings in ASL MRI studies of AD[27]. Reduced perfusion of the posterior cingulate predicts conversion from MCI to AD[28]. In contrast we found increased perfusion in the posterior and anterior cingulate in the *APOE* 4+ group. We also found marked hyperperfusion in left frontal and parietal regions in the *APOE* 4+ group; we did not find previous studies which reported this finding, though intriguingly, hypoperfusion in parietal and frontal regions has been widely reported in MCI, AD and to a lesser extent in cognitively-normal older adults[12,29].

Carrying an *APOE* 4 allele is known to increase the risk of developing AD and to lower the age of onset of cognitive decline. *APOE* 4 is involved in cerebrovascular function and is associated with a range of vascular conditions including arteriosclerosis and amyloid

angiopathy[30]. It is generally accepted that hippocampal atrophy with a relative lack of whole brain atrophy is associated with *APOE* 4[31], however, the relationship between brain perfusion and *APOE* status is not as clear. Previous studies suggest that the effect of *APOE* may be modified by other factors such as age or disease severity. For example, Kobayashi et al.[32] found an impact of *APOE* 4 on CBF in those with moderate AD but not mild or severe disease while Wierenga et al.[10] found that *APOE* 4+ individuals demonstrated relatively increased anterior cingulate perfusion in young adulthood and relatively decreased anterior cingulate perfusion in old age. It may be that increased cerebral blood flow in *APOE* 4 carriers contributes to the pathogenesis of the disease in its early stages, for example, by aiding the seeding of tau and amyloid, accelerating the degenerative process. Increased neural connectivity which is related to increased cerebral perfusion has been found to be associated with higher tau and amyloid burden in AD[33]. Alternatively it may be that hyperperfusion prior to the onset of clinical symptoms reflects some sort of ‘compensatory’ mechanism, i.e. supporting normal cognitive function in brains at early stages of neurodegeneration, as suggested for example by Ding et al.[29]. In support of this theory are the findings of Zlatar et al.[34] who found a relationship between increased CBF and poorer verbal memory in cognitively-normal *APOE* 4 carriers. In our cohort we did not find any correlation between CBF and cognitive test scores; the only group difference in cognitive performance was in the narrative recall task in which the *APOE* 4+ group (who had areas of increased regional CBF) performed slightly better than the *APOE* 4- group.

In their reviews Wierenga et al.[30] and Zhang et al.[35] discussed the implications of previous ‘paradoxical’ findings of both relative cerebral hypo- and hyperperfusion in ‘at risk’ individuals, which appear to be related to how the relationship between CBF and risk factors (e.g. vascular or genetic) is modified by age. Zhang et al. describe a pattern in which, following a peak in early adulthood, CBF gradually declines with age but is modified by lifestyle and risk factors; in *APOE* 4 carriers a second peak is described in middle-age[35], followed by a decline sharper than that of non-carriers as the individual moves into older age. The capillary dysfunction model of AD provides an explanatory framework for such a pattern. Østergaard et al.[36] describe an evolving relationship between regional CBF, capillary permeability, capillary surface area, and capillary transit time heterogeneity. According to this model, the neurovascular changes that accompany AD (e.g. increasing blood vessel tortuosity) predict that an increase in CBF would be seen in pre-symptomatic

AD; switching to a decrease in CBF part way through the subclinical phase and markedly decreasing as dementia progresses. According to this theory our findings of regional hyperperfusion in those at high risk of AD could reflect a very early marker of neural and vascular dysfunction.

An alternative explanation for areas of relative hyperperfusion in the *APOE* 4+ group is that in younger age the *APOE* 4 allele confers (or is related to) beneficial effects on brain function and memory. For example, Mondadori et al.[37] found that some aspects of cognition were better in young, healthy *APOE* 4 carriers. This theory would not be supported by the common finding that lower educational attainment is associated with AD; although this association has not been found universally and many individual and social factors influence educational attainment aside from innate cognitive ability[38]. In our cohort minimal group differences were seen in terms of cognitive test results; there was no difference in cognitive test results between the FH groups but the *APOE* 4+ group performed slightly better in the narrative recall task. We did not find a correlation between individual regional CBF and cognitive test results, therefore our findings would not support the theory that *APOE* 4 has a beneficial effect on some aspects of cognitive function via an increase in regional cerebral perfusion.

We found that regional hyperperfusion was more widespread when we defined the groups by *APOE* status rather than FH. When we included *APOE* status as an additional covariate the group difference between FH + and - was much reduced, however some areas of hyperperfusion in left temporal, parietal and frontal regions persisted. This implies that these effects on perfusion are not being driven by *APOE* 4 alone and that some familial or environmental risk factor aside from *APOE* 4 is playing a role. The greatest effect size was seen in the left lateral temporal region in the FH+ group and in left cingulate and left lateral frontal and parietal regions in the *APOE* 4+ group. The regional patterns of hyperperfusion are similar but not identical; it may be that pathologies in different brain regions or in different individuals will ultimately be explained by different causative mechanisms. *APOE* 4 is not the only genetic variant known to be associated with sporadic AD risk; thousands of common genetic variants which increase dementia risk have been identified via genome-wide association studies (GWAS)[39]. There is emerging evidence that these variants may contribute to AD risk via changes to vasculature[11]. The significant difference in DRS

between FH+ and FH- groups (which is not accounted for by *APOE* status) suggests that the additional risk conferred by FH may be bestowed via increased cardiovascular risk.

Strengths and limitations:

A major strength of our study is the number of participants and the richness of the data collected; a review of the literature revealed few studies of comparable size. The data reported here is pilot baseline data; the data will continue to grow richer as further baseline and follow-up data becomes available over the next 3 years. Neurodegenerative dementias such as AD develop over the years and decades prior to the onset of clinically significant symptoms, therefore large, longitudinal cohorts like the PREVENT-Dementia cohort are invaluable; ultimately allowing us to describe how brains change structurally and functionally as individuals move through middle to older-age, with a proportion going on to develop MCI and dementia.

In the PREVENT-Dementia study dementia risk is defined using FH and *APOE* 4. The causes of AD are multifactorial including both genetic and lifestyle factors[39,40]; genotyping in the study is limited to *APOE* analysis, therefore, we cannot explore the effects of broader genetic risk and the relationship between this risk and CBF.

The group difference in CBF between FH groups was largely explained by *APOE* 4. Although the parental dementia diagnoses were primarily reported to be AD or mixed AD and vascular (70.4%), our sample contains parental dementia diagnoses other than AD (such as vascular dementia and Frontotemporal dementia). Parental dementia subtype is a self-reported measure within the cohort and due to participant reporting errors or diagnostic uncertainty, the cohort may be more (or less) heterogeneous than reported. It may be therefore, that the effect of FH would become more marked in a larger (or more homogenous) cohort.

Conclusions:

We found areas of regional cerebral hyperperfusion in *APOE* 4+ compared to *APOE* 4- when corrected for age, gender, years of education and FWE. Our findings broadly contrast with those reported in studies of individuals with MCI and AD but align somewhat with previous literature concerning younger cognitively normal individuals at high risk of developing dementia. The significance of such findings is not yet clear and different theories

could be proposed to account for them. In this paper we have postulated that hyperperfusion in high risk individuals may contribute to the pathogenesis of AD, may reflect a 'compensatory' mechanism (in which the brain is working 'harder' to compensate for early neural damage), or may be a marker of early neural 'dysfunction' in individuals who are likely to develop AD. Further longitudinal data, including even earlier imaging, is indicated to determine at what point before dementia onset perfusion increases and will help us to understand its origins and implications. Examination of the full PREVENT-Dementia cohort and longitudinal follow-up of this cohort will address the limitations of this analysis.

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Conflicts:

JOB has no conflicts related to this study. Unrelated to this work, he has received honoraria for work as DSMB chair or member for TauRx, Axon, Eisai, has acted as a consultant for Lilly and has received honorarium for talks from GE Healthcare and research support from Alliance Medical.

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Recruitment:

Participants were recruited at West London Mental Health National Health Service (NHS) Trust (now known as West London NHS Trust) and scanning was carried out at the Clinical Imaging Facility, Imperial College London.

Ethics:

Patient consent for publication Not required.

Ethics approval NHS Research Ethics Committee London Camberwell St-Giles (REC reference: 12/LO/1023).

FIGURE LEGENDS:

Figure 1: scan inclusion/ exclusion pathway

Figure 2: Areas with significant increased cerebral blood flow in APOE 4 + vs - when corrected for age, gender and years of education. Scale shows TFCE clusters with FWE-corrected significance levels between $p=.01$ and $p=.05$.

Figure 3: Areas with significant increased cerebral blood flow in FH+ vs FH- group when corrected for age, gender and years of education. Scale shows TFCE clusters with FWE-corrected significance levels between $p=.01$ and $p=.05$

Figure 4: Areas with significant increased cerebral blood flow in FH+ vs FH- group with additional correction for APOE status (also corrected for age, gender and years of education). Scale shows TFCE clusters with FWE-corrected significance levels between $p=.01$ and $p=.05$

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